Ann Ist Super Sanità 2019 | Vol. 55, No. 2: 179-185
DOI: 10.4415/ANN_19_02_10

Unproven stem cell therapies: is it my right to try?

Luciana Riva[1], Laura Campanozzi[2], Massimiliano Vitali[3], Giovanna Ricci[4] and Vittoradolfo Tambone[2]

[1]*Unità di Bioetica, Istituto Superiore di Sanità, Rome, Italy*
[2]*Istituto di Filosofia dell'Agire Scientifico e Tecnologico – FAST, Università Campus Bio-Medico di Roma, Rome, Italy*
[3]*Policlinico Universitario Campus Bio-Medico, Rome, Italy*
[4]*Scuola di Giurisprudenza, Università degli Studi di Camerino, Camerino, Italy*

Abstract

Background. Nowadays one of the most critical aspects of innovative cell-based therapies is the unregulated industry, as it is becoming a *competitor* of the regulated system. Many private clinics, worldwide, advertise and offer cell-based interventions treatments directly to the consumer and this poses a risk to both vulnerable patients and health systems. Several countries have implemented Compassionate Use Programmes (CUP) that provide patients with medicines that have not yet completed the approval pathway, in the event that no reasonable alternative exists. Recently, in the public discourse, compassionate use has been increasingly associated with a patient's right to try. Thus, the aim of this study was to assess public knowledge of the clinical trials process with specific reference to innovative stem cell treatments, and trust in the institutions responsible for regulatory activities. We also asked people about their "right" to use unregulated therapies.

Methods. We developed an *ad hoc* questionnaire on three main areas of concern and administered it to 300 people in the patient waiting room at an Italian university hospital.

Results. Our findings suggest that people have a good knowledge of the clinical trials process and trust in healthcare institutions. Nonetheless, one person in two believes it is a right to use unregulated therapies.

Conclusions. We stress the need, in the age of cellular therapies, for a commitment to support vulnerable patients and to strengthen awareness among the public about the substantial boundary that differentiates *experimental therapies* from *unproven therapies*. There should not be a "right to try" something that is unsafe but rather approved treatments and in line with good clinical practice. The trend, which emerged on this issue from our study, is quite different, confirming the urgent need to improve health information so that it is as complete as possible.

Key words

- stem cells
- compassionate use trials
- trust
- medical tourism

INTRODUCTION

Worldwide, innovative cell-based therapies have represented a considerable challenge for regulatory systems over the last decade. Within this field characterized by a rapid technological advancement, the products of the discoveries of medicine and biology have become more and more "therapeutic options" advertised and offered by private producers directly to the consumer. Over the last two decades, a boom in for-profit clinics offering stem cell therapy directly to patients for a wide range of diseases has occurred and tragically, some patients died from dangerous injections of cells [1].

Within a regulated context, the responsibility for the assessment of safety of treatment pertains to regulatory agencies; outside this setting, patients do not have an adequate guarantee of protection. The European Committee for Advanced Therapies (CAT) has expressed its views on this matter in many documents, with particular "concern about a phenomenon known as stem-cell tourism in which severely ill patients travel to clinics around the world where unauthorized stem-cell-based treatments are offered in the absence of rigorous scientific and ethical requirements" [2]. The CAT has strongly encouraged the development of stem-cell-based medicinal products in approved and high-quality research programs [3].

The protection of patients from ineffective and risky therapies is an important issue that requires legal, ethics and public health considerations. Currently, most stem cell therapies are experimental and many scientists do

Address for correspondence: Luciana Riva, Unità di Bioetica, Istituto Superiore di Sanità, Via Giano della Bella 34, 00162 Rome, Italy. E-mail: luciana.riva@iss.it.

not know exactly how they work and how safe they are. In turn, the clinical application of these products, which has only just begun, is raising numerous ethical questions that the International Society for Stem Cell Research (ISSCR) has recently examined in detail in the "Guidelines for Stem Cell Research and Clinical Translation" [4, 5]. Specifically, the transparency of the clinical data, the accurate and effective communication in the process of informed consent are crucial elements, especially in the early phase of trials with humans, when there should be particular care in avoiding overestimation of benefits or therapeutic misconceptions [5]. For example, people may not clearly understand the significance that a regimented experimentation process assumes for the safety and protection of health and may be confused about the readiness of a technology for clinical application.

In the era of biotechnologies and great attention of media to these new therapies, which often creates disproportionate hope among people, these considerations are highly relevant for their implications. Patients and their families, especially if they have a very serious health condition, are vulnerable and must be protected as such. For the first time, the Guidelines focus on the importance of the communication process to the public, recommending timely correction of every possible misleading public representation. Inaccurate portraits of stem cell research may have severe consequences, including misinforming policy debate, and premature clinical use of unapproved treatments [6, 7]. An integrated effort is needed involving diverse actors, such as researchers, institutions and specialists in scientific communication to safeguard the public from misinformation.

The right to health

Stem cell therapies have become a matter of controversy in public debate and in legal decisions. There have also been cases in which patients opposed the State for access to experimental therapies. In 2014, Italy was the subject of a highly controversial legal battle, Durisotto *vs* Italy, also known as the "Stamina case", about an alleged innovative stem-cell therapy. The controversial and broad debate that developed around this case focused on the acceptability of providing treatment not based on scientific evidence when a patient's request is advanced as a last hope of healing or relief from a condition of suffering. The stamina treatment, which had been administered to numerous patients starting in 2008 in public hospital, was based on the use of mesenchymal stem cells (MSCs) and intended for the treatment of neurodegenerative diseases. Unfortunately, as was then demonstrated, there was no study protocol upstream, with one exception which presented serious flaws and omissions involving a procedure which did not comply with any Good Manufacturing Practices (GMP) [7, 8].

On 6 May 2014, the European Court of Human Rights (ECHR) ruled on the patient's right to decide to resort to unproven treatments – stem cell therapies – in the absence of other therapeutic possibilities, in the wake of the Durisotto *vs* Italy case. Mr. Durisotto applied to the ECHR following the refusal by the Italian courts to authorize compassionate therapy (specifically, the "Stamina" method) to treat his daughter's degenerative cerebral illness. The European Court rejected the patient's claim. In particular, it declared the application inadmissible under Article 8 of the European Convention on Human Right (right to respect for private and family life) stating that "the interference in the right to respect for the private life, represented by the refusal to grant the request for medical therapy, could be considered as necessary in a democratic society". The prohibition on access to the therapy in question "pursued the legitimate aim of protecting health and was proportionate to that aim" [9].

If the protection of the right to health is attributed to the legislator, access to a new therapy has to be regulated by healthcare norms that define all the conditions of the procedure. In other words, healthcare authorities must decide on the scientific validity and on the appropriateness of the treatment.

In media discourse, the reference to *compassion*, *hope* and *right* are often invoked and associated with the request for access to innovative or experimental procedures. As we will see later, the definition "compassionate use", used today even within institutional and regulatory documents, can be easily misunderstood regarding its exact meaning [10, 11]. However, in no way does it indicate the possibility of accessing any treatment offered by anyone without prior sharing of the rationale within a broader scientific community. It does not mean that any attempt is admissible: a choice made on the emotional wave of *despair* and *hope* may not be the best choice and could even be detrimental to the dignity of the person's own life if, for example, it involves avoidable or disproportionate suffering.

The Right To Try (RTT) movement

In recent years, many US States, in the face of great pressure from public movements, patient advocacies and think tanks, have passed "Right to Try" laws, which give terminally ill patients access to experimental compounds that have passed phase I testing [12]. These laws provide that a patient who wants to try an experimental drug can contact the pharmaceutical company directly, cutting out the "filter" of the competent authority, the Food and Drug Administration (FDA). Those against the Right to Try (RTT) laws generally argue that they are not a boon for patient rights, but that they rather dismantle the safety system that protects people. Liberal access to unproven therapies could have a negative impact on individual patients in a state of vulnerability, by offering false hope that leads to increased suffering. In the US, supporters of the RTT have used emotionally charged stories in which someone is dying – a child or parent – to invoke access to an experimental drug that might offer salvation. If there is hope that the treatment might work, RTT supporters argue, the patient has the right to try to preserve his own life. However, patients in very serious condition might judge risks and potential benefits differently than scientists do and they might not sense the irrationality of their own hope.

It should be noted that RTT laws offer not a right to try, as suggested in the name, but rather a right to

ask for access in order to try. To acclaim and advocate a right to try suggests that regulated systems do not permit access to experimental treatments, whereas in many countries, these systems provide compassionate use or expanded access of experimental treatments by defining a threshold of scientific evidence and safety necessary to support such use or access. In this regard, it is useful to stress that there is a difference between *unproven therapies* and *unregulated therapies* and that the treatments administered through compassionate use or expanded access programmes are unproven (i.e. not yet proven) but regulated. Around this issue, a radical idea of care as free choice – with no interference whatsoever – to make decisions regarding one's body seems to be emerging. Some authors have referred to a "right to self-medication", by rooting this right in the value of *autonomy* [13].

This radical position reflects either a feeling of distrust in institutions that must protect the interests of patients or a more generic statement of freedom of choice. Perhaps for some it is a mixture of the two. The basic question is: to what extent should the law prevent people from taking risks they voluntarily accept. For some, protection at all costs is considered paternalistic, a stance that disregards the value of autonomy of the individual.

Regarding these issues, the position expressed by the ECHR in Durisotto *vs* Italy is very clear. It is useful here to point out three facts:

- the ECHR reiterated that it was not to the place of the international court to substitute itself for the competent domestic authorities in determining the level of acceptable risk for patients wishing to have access to compassionate therapy in the context of experimental treatment;
- the ECHR stated that "The interference in the right to respect for one's private life, represented by the refusal to grant the request for medical therapy, could be considered as necessary in a democratic society";
- the protection of the right to health, on the part of the legislator, is realized through the non-authorization of unsafe or harmful treatments.

Compassionate use program

Regulation no. 726 /2004 of the European Parliament and Council regulates "Compassionate use", which it defines in art. 83, part 2 as "making a medicinal product (…) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease (…) and who cannot be treated satisfactorily by an authorized medicinal product" [14]. In turn, the European Medicines Agency (EMA) defines "compassionate use" as a treatment option that allows the use of an unauthorized medicinal product, which is under development. In Europe, EMA provides recommendations and guidelines for compassionate use [15] and every member state sets its own rules. Currently, a wide disparity exists across European member states regarding the procedures of application [16, 17].

Italian law allows compassionate use in some circumstances in which specific criteria are met. DM 7/09/2017 on "Therapeutic use of a medicine subjected to clinical trials" regulates access to experimental pharmacological therapies for use outside a clinical trial, to patients suffering from serious, rare or life-threatening diseases when, according to the clinician, there are no other valid therapeutic alternatives [18].

Innovative therapies, by their nature, are experimental treatments which cannot be evidence-based or clinically indicated and may lack a demonstrable safety profile. As some authors have highlighted, the primary purpose of legislation on innovation, and on medical innovation in particular, must be to benefit the individual patient [19]. To conduct an open debate on how to guarantee "responsible innovation" at a time when innovation in cell therapy and regenerative medicine is moving into the clinical context is an issue of paramount importance. Equally important is the need to increase public awareness of the significance of the regulated process of clinical experimentation and trust in institutions responsible for the control, approval and evaluation of the risk-benefit profiles of innovative treatments. Against this backdrop, we have conducted a pilot survey on a sample of the Italian population to assess public knowledge of the clinical trials process with specific reference to innovative stem cell treatments. We also asked people about their "right" to use unregulated therapies, in order to get a picture of how people are potentially vulnerable to undergoing unproven therapies and to have some indication of what the right to try means for them.

MATERIALS AND METHODS

A bibliographic search in the PubMed database was conducted to verify the presence of international studies on attitudes among the public towards both the use of unregulated therapies and general knowledge of the clinical trial process. No questionnaires related precisely to our query was found. We chose to carry out a survey on a sample of the population using an *ad hoc* questionnaire developed through the methodology of an expert focus group. Five experts took part in the focus group: a bioethicist, a bio-statistician, a philosopher of science, an expert in health professions and a psychologist. The issues that emerged from the working group discussions were divided into three conceptual blocks representing three topics under investigation: 1) public information on the clinical trial process; 2) specific information on treatments based on stem cells; 3) general trust in the governing bodies and institutions responsible for the control and regulation of the clinical trial process. Based on the experts' suggestions, we formulated ten questions for each thematic area and then asked the focus group members to indicate through a vote the most effective ones. The resulting questionnaire used for the survey consisted of 16 questions (6 for the first block, 4 for the second and 6 for the third), with an introductory section consisting of five items for sample stratification (sex; age; level of education; work in the health sector or not; medical sector in which the patient was seeking care). The sample for the study was randomly recruited among people who were in the patient waiting room at the Campus Bio-Medico University Hospital in Rome, Italy. The

questionnaire was distributed to a total of 300 people including patients and "companions" (persons accompanying patients). The questionnaire was anonymous and the estimated compilation time was approximately 4 minutes. Participants could stop filling out the questionnaire at any time. The data extrapolated from the returned questionnaires was placed in an electronic database built specifically for collection. The data was verified and analysed through the statistical package SPSS v24 copyright. A first descriptive analysis was conducted for each individual item. Then we proceeded to make comparisons among the responses to the various items by using the chi-square test. Differences with P <0.05 were considered statistically significant. When answers to different questions are been examined, the frequency of the correct answers is compared with the sum of the frequencies of the wrong answers across the different questions. The significant results of the study are reported and discussed in the next section.

RESULTS

A total of 219 questionnaires were returned (73% of the total responded). The descriptive analysis showed that the sample is homogeneous as regards the stratification variables with the exception of the level of education (67.12% of the sample had completed high school but not studied beyond that) and the type of occupation (86% of the responders are not healthcare professionals) (*Table 1*). On the questions concerning knowledge of the clinical trial process, 77.63% of the sample showed that they knew what a clinical trial is, answering that it is a study authorized by the institutions responsible for public health policies. 74.43% correctly answered the question about whether an investigational drug can be administered to humans. 52.05% answered that the experimentation of a new drug or treatment lasts on average from 7 to 10 years. The data showed that those who correctly answer questions about the clinical trial process have much more confidence that regulation protects the interests of patients compared to those who have no knowledge of the trial processes (P <0.05). Only 33.33% of the sample knew the meaning of "compassionate use" of a drug and 52.51% responded that they did not know if such use is possible in Italy. To the question "Do you think it is a right of patients to use treatments not authorized by the institutions responsible for public health policies", 43.38% of the sample replied no, 41.55% yes and 15.07% did not know. 95.89% of the sample responded they had heard of stem cell-based treatments. Answers to the question about the possibility of using stem cell-based treatments in Italy were homogeneously distributed (36.99% yes; 29.22% no; 33.79% I do not know). When asked about the number of pathologies for which stem cell treatments have proven effective, 42.47% responded "I don't know", 22.83% responded "more than 100 pathologies" and 33.79% responded "a very small number of pathologies". 72.60% of the sample said they have heard of patients going abroad to undergo treatment with stem cells not authorized in Italy. The analysis showed no significant correlation between the opinion about the use of unregulated drugs and the medical sector in which the patient was seeking care. Answers regarding trust in the institutions responsible for regulatory activities were positive in reference to the following: Italian Medicine Agency (AIFA) 75.9%; Ministry of Health 71.3%; Italian National Institute of Health (Istituto Superiore di Sanità – ISS) 79.9%; World Health Organization (WHO) 89.5%; Ethics Committees 76.3%. In addition, a statistically significant correlation was found (P <0.05) between responses to the question on trust in institutions and the question of trust in the fact that regulation of the process protects the interests of patients (*Table 2*). Only 12 of the 16 items in the questionnaire are shown in the table. We decided to omit four questions related to the third block because they showed no significant correlation. We believe this is probably due to the complexity of the construct formulation.

Table1
Overview of the responders to the pilot survey on the public's knowledge about. perception of. and trust in the testing process of a new drug or treatment

Characteristics	
Total (N)	219
Sex (%)	
Female	50.68
Male	49.32
Age (Mean, min-max)	
Male	40 (18-82)
Female	44 (19-80)
All	42 (18-82)
Education (%)	
None	1.37
Primary school	5.02
Secondary school	67.12
University (undergraduate)	22.83
Master/PhD	3.66
Occupation in healthcare setting (%)	
Yes	14.16
No	85.84
Type of respondent (%)	
Patient	43.38
Companion	56.62
Medical field of the the patient's appointment (%)	
Diagnostic	58.90
Surgical area	22.84
Onco-hematologic	18.26

DISCUSSION

The results show that the people interviewed had a good general knowledge of the clinical trial process. In fact, the number of correct answers to the questions

Table 2
Answers to the questionnaire items divided by thematic blocks

Blocks	Final number (%)
Total	219
Block 1 **What is in your opinion a "clinical trial"?**	
A study authorized by the institutions responsible for public health policies	77.62
A study not yet authorized by the institutions responsible for public health policies	15.53
The administration of an innovative drug or treatment outside of a hospital facility	5.02
I don't know	1.83
Is it possible to administer an investigational drug to human beings?	
Yes	74.42
No	15.53
I don't know	10.05
How long do you think the testing process is for the development of a new drug or treatment ?	
Two/three months	1.37
One year	30.14
Between seven and ten years	52.05
I don't know	16.44
Which of the following definitions of "compassionate use" of a drug is, in your opinion, most correct?	
Use of a drug outside the testing process	10.97
Use of a drug outside the national regulatory procedures	21.00
Use of a drug while the trial is not over yet	33.33
I don't know	34.70
Is the compassionate use of a drug possible in Italy?	
Yes	17.35
No	30.14
I don't' Know	52.51
Block 2 **Have you ever heard of stem cell treatments?**	
Yes	95.89
No	1.37
I don't know	2.74
In Italy it is possible to use stem cell therapy?	
Yes	36.99
No	29.22
I don't know	33.79
Are there diseases for which stem cell treatments have proven effective?	
Yes. more than a hundred different diseases	22.83
Yes. a very small number of diseases	33.79
No	0.91
I don't know	42.47
Have you ever heard of patients who travel to foreign countries to undergo stem cell-based treatments that are not authorized in Italy?	
Yes	72.60
No	27.40
Do you believe it is a right of patients to use treatments that have not been authorized by the competent authorities?	
Yes	41.55
No	43.38
I don't know	15.07
Block 3 **You can vote from -3 to +3 (-3 = no trust +3 = great trust) to express your confidence in regulatory activity of clinical trials of the following institutions***	
Italian Medicines Agency (AIFA)	75.8
Ministry of Health	71.3
Italian National Institute of Health (ISS)	79.9
World Health Organization (WHO)	89.5
Ethical Committees	76.3
*The percentages were calculated by summing the positive opinions, from 0 upwards.	
Do you think that in Italy the regulation protects the interests of patients?	
Yes	43.01
Not	56.98

related to this thematic area is significantly high, with the exception of the questions on the meaning of "compassionate use". These responses correlate with the perception of protection by the institutions that regulate the process suggesting that good information could increase the degree of trust in people. The recent 2018 Edelman Trust Barometer seems to confirm this position in showing a dramatic distrust mainly at the media level, due to the lack of reliability of and transparency in information [20]. The data also shows that the meaning of the "compassionate use" procedure is not well known to the population, suggesting that in this field general information about the possibilities of access to experimental treatments, in a regulated manner, need to be improved.

Regarding the right to use unregulated treatments, responses were homogeneously distributed between the belief that it is a patient right to use treatments outside of a regulation and the belief that it is not. These responses have no correlation with the answers regarding knowledge of the experimentation process. It seems that the perception of this "right" is independent of the degree of information about and trust in the institutions: correct information does not seem to influence opinion. It would be useful to study more in depth the question of "patients' right", to see if when responding to the question on "right", people understand the term as a general right to access to compassionate use (about which they do not seem to have sufficient information) or as a general right to try any treatment regardless of whether it is located within or outside a shared and regulated path. About stem-cell based therapies, the respondents in general did not have a good understanding of how these therapies are regulated and the real possibilities of use, although the vast majority of them had heard of it. The fact that one out of three people is unaware that in Italy it is possible to use stem cell-based treatments, provided within a regulated process, explains in part the misunderstanding we have discussed above. The same misunderstanding is implicit in US "Right To Try" movements, namely that regulators do not contemplate a right to try innovative treatments in specific circumstances. Information in this sense must certainly be expanded and managed responsibly and transparently to avoid the risk that patients find themselves alone in seeking life-saving treatments at a time when they are extremely vulnerable. Interestingly, 72% of the sample had heard of patients going abroad to undergo treatments unauthorized in Italy.

CONCLUSIONS

Our sample shows a good general knowledge of the regulated process of developing new drugs and treatments and a strong confidence in the institutions responsible for the control. At the same time, it shows a lack of knowledge about the regulation of innovative treatments based on stem cells. Probably, in this field, alongside media overexposure, there has not been sufficient institutional communication. In our view, it is very important that there be a multi-level commitment to increase awareness among the population of the possibility of using innovative treatments, even if the formal testing process has not been completed yet, and that unregulated treatment, often offered without guarantees, is very different from the compassionate use or hospital exemption of a product. The "Right to Try" movements in the US, by using the word "right", implicitly suggested that a right to try is denied within the regulated system, whereas what is denied is exclusively use that is not secure, ineffective and that exposes the person to unreasonable risks.

Within a regulated system, compassionate use procedures can be improved to allow easier or faster patients access, but this is a different matter. The possibility of relying on risky therapies whose validity is not recognized can perhaps be viewed by some as a right, within the conceptual framework of personal autonomy and freedom of choice. In our view, the right to try something whose level of safety and/or risk has not been previously considered acceptable and that does not follow a protocol in line with good clinical practice is not sustainable. Furthermore, autonomy and free choice cannot be considered as such where there is inadequate information and thus the State and the medical community in general have, at the least, a moral duty to educate people through real information about the risks they run. The lack of awareness and comprehension affects dramatically the possibility of free choice, especially in situations of strong vulnerability. Transparent and effective communication on how to access clinical trials, and on available treatment possibilities, within the doctor-patients relationship as well as within the institution-citizen relationship is a preventive act to protect the vulnerable population.

A limitation of this study lies certainly in the size of the sample that does not allow us to make inferences about the general population. It provides, however, some useful food for thought for further research aimed at widely exploring the dimension of people's views on innovative therapies, the theme of building a relationship of trust, founded primarily on responsible and transparent communication, and the empowerment of people in the era of cell therapy and regenerative medicine.

Author's contribution to the manuscript

LR and VT: conceptualization and methodology; LR: investigation; LR, LC and GR: writing the draft and the original article; LC and MV: formal analysis and data curation.

Acknowledgments

The authors wish to thank E. Cella for her assistance with the data analysis.

Conflict of interest statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Received on 9 January 2019.
Accepted on 13 May 2019.

REFERENCES

1. Lysaght T, Lipworth W, Hendl T, Kerridge I, Lee TL, Munsie M, et al. The deadly business of an unregulated global stem cell industry. J Med Ethics. 2017;43:744-6.
2. Committee for Advanced Therapies and CAT Scientific Secretariat. Use of unregulated stem-cell based medicinal products. The Lancet. 2010;376:514.
3. Committee for Advanced Therapies (CAT). Reflection paper on stem cell-based medicinal products. CAT; 2009. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079932.pdf.
4. International Society for Stem Cell Research (ISSCR). Guidelines for stem cell research and clinical translation. ISSCR; 2016. Available from: www.isscr.org/guidelines2016.
5. Frati P, Scopetti M, Santurro A, Gatto V, Fineschi V. Stem cell research and clinical translation. A roadmap about good clinical practice and patient care. Stem Cells Int. 2017. Article ID 5080259. Available from: http://doi.org/10.1155/2017/5080259.
6. Kimmelman J, Hyun I, Benvenisty N, Caulfield T, Heslope HE, Murry CE, et al. Policy. Global standards for stem-cell research. Nature. 2016;533:311-3.
7. Solarino B, Laforgia M, Dell'Erba A, Laforgia N. Stem cell therapy: medico-legal perspectives in Italy. Front Cell Neurosci. 2015;9:240.
8. Abbot A. Leaked files slam stem-cell therapy. Nature. 2014;505:139-40.
9. European Court of Human Rights. Durisotto vs. Italy. ECHR 153 (2014) 28.05.2014. Available from: https://hudoc.echr.coe.int/eng#{%22itemid%22:[%22001-144670%22]}.
10. Borysowski J, Ehni HG, Górski A. Ethics review in compassionate use. BMC Med. 2017;15:136.
11. Comitato Nazionale per la Bioetica, Cura del caso singolo e trattamenti non validati (c.d. "uso compassionevole"). 27 febbraio 2015. Available from: http://bioetica.governo.it/media/170732/p119_2015_cura_del_singolo_trattamenti_non_validati_it.pdf.
12. Dresser, R. "Right to Try" Laws: The gap between experts and advocates. Hastings Center Report. 2015;45:9-10.
13. Flanigan J. Three arguments against prescription requirements. J Med Ethics. 2012;38: 579-86.
14. European Union. Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004, Official Journal of the European Union. Available from: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp&mid=WC0b01ac05809f843c.
15. European Medicines Agency (EMA). Guideline on compassionate use of medicinal products, pursuant to article 83 of Regulation (EC) No 726/2004. Available from: www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf.
16. Whitfield K, Huemer KH, Winter D, Thirstrup S, Libersa C, Barraud B, et al. Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries. Trials. 2010;11:104.
17. Balasubramanian G, Morampudi S, Chhabra P, Gowda A, Zomorodi B, Gayathri et al. An overview of compassionate use programs in the European Union Member States. Intractable Rare Dis Res. 2016;5:244-54.
18. Decreto Ministeriale 07/09/2017. Disciplina dell'uso terapeutico di medicinale sottoposto a sperimentazione clinica. Available from: www.aifa.gov.it/sites/default/files/DM_7SETTEMBRE2017_0.pdf.
19. Samanta J, Samanta A. Quackery or quality: the ethico-legal basis for a legislative framework for medical innovation. J Med Ethics. 2015;41(6):474-7.
20. Edelman Trust Barometer. Global Report. Available from: https://cms.edelman.com/sites/default/files/2018-01/2018%20Edelman%20Trust%20Barometer%20Global%20Report.pdf.